Air Pollution, Asthma, and Sleep Apnea: New Epidemiological Links?

Gökhan M. Mutlu, M.D.¹, and Yüksel Peker, M.D., Ph.D.^{2,3,4*}

¹Department of Medicine, Section of Pulmonary and Critical Care Medicine, The University of Chicago, Chicago, Illinois; ²Department of Pulmonary Medicine, Koc University School of Medicine, Istanbul, Turkey; ³Department of Clinical Sciences, Respiratory Medicine and Allergology, Faculty of Medicine, Lund University, Lund, Sweden; and ⁴Division of Pulmonary, Allergy, and Critical Care Medicine, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania

ORCID IDs: 0000-0002-2056-612X (G.M.M.); 0000-0001-9067-6538 (Y.P.).

Air pollution results from the release of harmful or excessive quantities of substances into the atmosphere. Air pollution is a complex mixture of gaseous (nitrogen dioxide [NO₂], ozone) and particulate (particulate matter [PM]) components, each of which has detrimental effects on human health (1). It is now well accepted that exposure to ambient (outdoor) air pollution increases morbidity and mortality and shortens the life span (1, 2). The World Health Organization estimates that exposure to ambient air pollution leads to 4.2 million premature deaths worldwide every year (3). The Global Burden of Diseases, Injuries, and Risk Factors Study 2015 identified air pollution as a leading cause of global disease burden and as the fifth mortality risk factor, particularly in low- and middle-income countries (2).

The majority of air pollution-induced morbidity and mortality is due to cardiopulmonary diseases, including asthma, chronic obstructive lung disease, lung cancer, congestive heart failure, and ischemic/thrombotic cardiovascular disease (myocardial infarction, ischemic stroke) (1, 2). In this issue of the *AnnalsATS*, two articles provide new insights into how air pollution causes cardiopulmonary morbidity (4, 5). In the first article, Hansel and

colleagues (pp. 348-355) evaluated the effect of air pollution on asthma in children (4). Although previous studies have already demonstrated a strong link between air pollution and asthma in children, they largely focused on the role of air pollution in exacerbations and health care utilization (6-8). Building on their previous study showing that children living in houses close to a main roadway with a higher traffic load had greater odds of asthma symptoms (9), Hansel and colleagues found that both PM_{2.5} (PM < 2.5 μm) and NO₂ were associated with greater odds of uncontrolled asthma (4). For each interquartile range increase in PM_{2.5} and NO₂ concentrations, the odds of uncontrolled asthma increased by 60% and 34%, respectively. Interestingly, the proportion of PM attributed to black carbon was also associated with increased risk of uncontrolled asthma. Correlating with the effect of air pollution on symptoms, both PM_{2.5} and NO₂ concentrations were associated with worse asthma-related quality of life, (QOL), which refers to the perceived impact that asthma has on the patient's QOL. Corroborating published data, the study has also shown that PM_{2.5} was significantly associated with increased use of health care utilization and missed school days.

Although the role of ozone, one of the gaseous components of air pollution, in asthma is well studied, there are only a few studies that investigated the potential impact of PM air pollution on asthma. Hansel and colleagues not only provide further evidence for the importance of PM air pollution in asthma but also extend its role beyond exacerbations to symptom control and asthma-related QOL (4). These findings are also particularly important as the authors studied children in Peru, which has a higher incidence of asthma among children and adolescents than other low- and middle-income countries, suggesting that PM air pollution may play a role in the asthma-related disease burden in Peru. However, as the authors elegantly pointed out, the study has several limitations, including the lack of data

on indoor exposure and ozone, both of which are important environmental risk factors that can affect asthma.

Despite growing clinical and experimental evidence linking PM air pollution with asthma, we do not know the mechanisms by which PM affects asthma. One of these mechanisms may be the ability of PM to elicit the release of proinflammatory cytokines such as interleukin-6 (IL-6) (10, 11), which may induce the differentiation of T-helper cell type 2 (Th2)/Th17 cells from Th2 cells leading to a switch to a Th2/Th17-predominant endotype, which is associated with worse asthma and steroid resistance (12). However, despite two-thirds of children having moderate to severely persistent asthma, only a minority (4%) were on long-term control medications such as inhaled corticosteroids. Therefore, the impact of air pollution on the possibility of inducing steroid resistance could not be evaluated. It is clear that further studies including other measurements, such as asthma endotype evaluation, are warranted to better understand how PM air pollution affects asthma. Furthermore, there is need for studies that will allow integrative analysis of exposure data with physiologic, genetic, and omics data to identify individuals who may be particularly at risk for PM-induced adverse health effects.

In the second article in this issue of the *AnnalsATS*, Billings and colleagues (pp. 363-370) evaluated the effect of chronic air pollution exposure on obstructive sleep apnea (OSA) and objective sleep disruption (5). Although there is increasing awareness regarding the influence of environmental factors on sleep, there has been limited research regarding the relationship between air pollution and sleep quality and OSA, an important risk factor for cardiovascular disease. The authors analyzed data from a sample of the Multi-Ethnic Study of Atherosclerosis (MESA), a longitudinal study of cardiovascular disease among 1,974 adults aged 45 to 84 years (average, 68 yr), who participated in the MESA Air

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and MESA Sleep Ancillary studies. Mean annual and 5-year exposure levels to NO₂ and PM_{2.5} were estimated at participants' homes using spatiotemporal models based on cohort-specific monitoring. Participants underwent in-home full polysomnography and completed 7 days of wrist actigraphy measurements.

The key finding in the study by Billings and colleagues was that chronic exposure to ambient air pollution was associated with OSA (5). Exposure to higher levels of NO₂ and PM_{2.5} was associated with greater odds of moderate to severe OSA (apnea-hypopnea index ≥ 15). Specifically, 10 ppb higher NO₂ (averaged over either 1 or 5 yr) and each increase of 5 $\mu\text{g}/\text{m}^3$ in annual mean PM_{2.5} were associated with 40% and 60% greater odds of OSA, respectively. However, PM_{2.5} exposure averaged over 5 years was not associated with OSA. This lack of association with 5-year average was attributed to possible adaptations that may be induced by chronic exposure to PM. Last, neither NO₂ nor PM_{2.5} levels had a significant impact on sleep efficiency. Nevertheless, the lack of significant effect of air pollution on efficient sleep should be interpreted cautiously, because the definition of reduced sleep efficiency was arbitrary ($\leq 88\%$, corresponding to the first quartile of the 7-day actigraphy average), and there were probably other environmental factors that

were not possible to control in the given 7-day period. As also acknowledged by the authors, other limitations of the study include the observational nature of the study, assessment of polysomnography at only one time point, limited evaluation of causality, and lack of a full understanding of how retrospectively determined exposure durations influence sleep.

Notwithstanding the limitations, the novel findings linking air pollution with OSA beg the question about the mechanisms by which air pollution affects sleep, control of breathing, and the upper airway. It is not surprising that air pollution may affect the upper airway, as it is the entry site for air pollutants. Air pollution has been previously associated with nasal inflammation, chronic rhinosinusitis, and upper airway inflammation, all of which may lead to increased upper airway resistance and consequently obstruction during sleep (13). Few studies suggested that air pollution may affect brain function, including cognitive and brainstem function (14); however, it is not known if exposure to air pollution can affect the respiratory center and control of breathing.

Current evidence suggests that air pollution induces adverse effects on the cardiovascular system via direct and indirect mechanisms. Air pollution

induces lung inflammation and release of proinflammatory cytokines, including IL-6, which can spill over into the bloodstream, leading to systemic inflammation, release of acute-phase reactants, and induction of a prothrombotic state (1). Air pollution also causes activation of the sympathetic nervous system and insulin resistance, leading to metabolic syndrome and diabetes mellitus (11, 15). Results from this and previous studies (16, 17) linking air pollution with OSA provide an additional mechanism for the association between air pollution with cardiovascular disease. Importantly, these findings also suggest that the effect of air pollution on the cardiovascular system is complex and mediated via many mechanisms that may also interact among themselves (i.e., interaction between OSA and the sympathetic nervous system and insulin signaling/resistance).

Taken together, the results of both studies emphasize that improving air quality may improve sleep and lung health and potentially decrease the prevalence and severity of asthma and OSA. Further studies will be needed to elucidate the importance of each mechanism leading to cardiovascular morbidity and mortality related to air pollution. ■

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